REMARKS

Reconsideration of the application is respectfully requested. Claim 20 has been amended to specify an initial treatment with citalopram. Support for claim 20 is found in the specification at, for example, page 1, lines 12-19; and page 5, lines 16-27. Claims 41-44 have been canceled, without prejudice or disclaimer. No new matter has been added. Claims 20-40 are pending and at issue.

Obviousness-Type Double Patenting

Claims 20-44 have been provisionally rejected for obviousness-type double patenting over claims 36-46 of U.S. Patent Application No. 10/468,685, claims 20-34 of U.S. Patent Application No. 10/644,587, and claims 20 and 22-37 of U.S. Patent Application No. 10/644,588, in view of Applicant's allegedly admitted prior art.

The rejection of claims 41-44 is moot because these claims have been canceled. The rejections over U.S. Patent Application No. 10/468,685 and U.S. Patent Application No. 10/644,587 are moot because these applications have been abandoned. Regarding the rejection over U.S. Patent Application No. 10/644,588, Applicant respectfully requests that this provisional rejection be held in abeyance because the conflicting claims have not yet been allowed.

Obviousness Rejection

Claims 20-44 have been rejected as obvious over U.S. Patent No. 4,943,590 ("Boegesoe") in view of the present specification. The Examiner cites Boegesoe as disclosing a method of treating depression using escitalopram, but admits that Boegesoe does not disclose the non-responsive patient population called for in the pending claims. According to the Examiner, it would have been obvious to administer escitalopram to treat depression in a patient who failed to respond to a non-escitalopram SSRI, such as citalopram, with a reasonable expectation of success because all SSRIs have the same mechanism of action.

The rejection of claims 41-44 is moot because these claims have been canceled. Additionally, claims 20-40 have been amended to specify an initial treatment with the SSRI citalopram.

Claims 20-40 are not obvious over Boegesoe because, *inter alia*: (i) the claimed method is associated with unexpected results that are entitled to consideration; and (ii) the efficacy of escitalopram in treating citalopram-resistant patients is surprising and unexpected because one of ordinary skill in the art could not have predicted the detrimental influence of R-citalopram in treating depression.

First, the presently claimed invention relates to a method of treating depression in certain treatment-resistant patients, specifically those who have not responded to treatment with citalopram. The surprising efficacy of escitalopram in such treatment-resistant patients is shown by the clinical study reported by Zimbroff, as discussed in the Response filed October 1, 2007. *See* Zimbroff, *Int. J. Neuropsychopharm.* 7(S1):S348, P02.164 (June 2004) (Poster presented at CINP2004; and Abstract). According to the Zimbroff study, the remission rate for patients treated with escitalopram after unsuccessful treatment with citalopram was 37%. *See* Zimbroff Poster (left column, Abstract and Results); *see also* Zimbroff Abstract (reporting remission rate of 42% for patients switched from citalopram to escitalopram). Thus, patients who did not respond to initial treatment with citalopram (a racemate, in which the active enantiomer is S-citalopram) surprisingly responded and even reached remission when treated thereafter with escitalopram (the individual active enantiomer).

The Examiner has refused to consider the unexpected results reported in Zimbroff, stating that arguments regarding this clinical study are "not persuasive because this abstract was published after the effective filing date of the instant application, therefore this study will not be considered. It is noted that the evidence must be a prior art showing unexpected results at the time of the invention in order to rebut a prima facie case of obviousness." Final Office Action at p. 7.

The Examiner's assessment of the law is incorrect. It is well established under U.S. patent law that later-published facts can be relevant to a nonobviousness argument and are therefore entitled to consideration. *See Kansas Jack, Inc. v. Kuhn*, 719 F.2d 1144, 1150 (Fed. Cir. 1983) ("Facts determinable at a later time may serve to evidence nonobviousness as of the time the invention was made."); *see also Richardson-Vicks Inc. v. The Upjohn Co.*, 122 F.3d 1476, 1483 (Fed. Cir. 1997) (referencing "the well-established rule that 'all evidence of nonobviousness must be considered when assessing patentability'") quoting *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995);

Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Co., 730 F.2d 1452, 1462 (Fed. Cir. 1984) (finding district court erred by ignoring evidence of unexpected results in assessing obviousness). The fact that Zimbroff's showing of unexpected results was published after the filing date of the instant application is irrelevant and certainly does not negate the value of these findings in the present obviousness determination. Moreover, the Zimbroff study confirms that escitalopram provides unexpected efficacy when used to treat depression in patients who failed to respond to citalopram, as presently claimed.

Second, the efficacy of escitalopram is particularly surprising for patients who were not successfully treated with citalopram, which is a racemate that contains both R-citalopram and escitalopram. As stated in the present specification, the inventors surprisingly discovered that the R-enantiomer in citalopram has a *negative* effect on escitalopram resulting in citalopram's inferior efficacy (*see* specification, p. 2, lines 13-14). This is demonstrated by the Zimbroff study, where escitalopram was found to be therapeutically effective while citalopram (at significantly higher doses, and in some cases three times higher) was not. None of the cited references discloses or suggests the detrimental influence of the R-enantiomer, or that administration of escitalopram alone would provide the demonstrated superior therapeutic effect over racemic citalopram.

Further, since Boegesoe discloses that "almost the entire 5-HT [serotonin] uptake inhibition [resides] in the (+)-citalopram enantiomer" (col. 2, lines 38-40), one of ordinary skill would not have expected escitalopram to have different efficacy than citalopram. At best, one of ordinary skill would have expected escitalopram to provide increased *potency* - i.e., achieving the same response in the patient, but requiring only half the dose to do so. In other words, when both the initial and later treatment contain the same active molecule (i.e., escitalopram) for providing an antidepressant benefit, one of ordinary skill would have had no reason to expect success with the later treatment after the initial treatment failed.

The unpredictability of individual enantiomers is well known in the art. The beneficial effects of a drug may reside in the racemic form or in one of its individual enantiomers; and there is no way to predict where the beneficial activity resides merely by assessing the structure of the molecule. There is also no way to predict what type of activity each individual enantiomer may possess. For instance, one enantiomer may exhibit favorable activity (e.g., antidepressant effects),

whereas the other may have no activity, some activity, antagonistic activity (e.g., against the active enantiomer), or a completely separate favorable or undesirable activity unrelated to that of the active enantiomer. *See, e.g.*, "Case Histories in Drug Discovery and Design 2001," *Drug News Perspect* 15(1):60-64, Jan-Fed 2002 at p. 62, left col. ("More than 500 drugs currently exist as racemates but perhaps only 5% are suitable. Unfortunately, the properties of the enantiomers are not predictable from the racemates.") (copy enclosed as Exhibit A).

This unpredictability was demonstrated in the case of fluoxetine (Prozac®), for example, which is an FDA approved racemic mixture of R-fluoxetine and S-fluoxetine. After determining that the R-enantiomer had a shorter and more desirable half-life, a study was conducted on the individual R-enantiomer. However, the results of this study showed that R-fluoxetine caused cardiotoxicity (a prolonged QT interval) that did not occur when administered in the racemic form. Hence, the more desirable enantiomer in Prozac® was *less* beneficial when administered in its enantiomerically pure form. *See* "Lilly pulls out of R-fluoxetine deal," *Scrip* 2586:24 (Oct. 25, 2000) (copy enclosed as Exhibit B); *see also Drug News Perspect* at p. 62, left col. ("[T]he properties of the enantiomers are not predictable from the racemates. For example, liver toxicity occurs with an enantiomer of **labetalol**, and QT prolongation occurs with **(*R*)-fluoxetine**.") (emphasis in original).

In view of the foregoing, claims 20-40 are not obvious; and Applicant respectfully requests that this rejection be withdrawn.

Conclusion

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining, which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

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Respectfully submitted,

By 

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